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Cadaver versus living donor kidneys: Impact of donor factors on antigen induction before transplantation

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Cadaver versus living donor kidneys: Impact of donor factors on antigen induction before transplantation.

Background. It is widely recognized that living-related donor (LRD) renal allografts have a higher overall graft survival than cadaver donor transplants. We tested the hypothesis that part of this is attributable to LRD kidneys being obtained under optimal conditions from healthy donors, whereas cadaveric kidneys may have experienced injury as a result of inflammatory events around the time of brain death.

Methods. We have performed a comparative immunohistochemical analysis of pretransplant donor biopsies from cadaveric ($N = 65$) and LRD ($N = 29$) kidneys to determine any differences that may predispose them to subsequent damage. Cryostat sections were stained with antibodies to leukocytes, adhesion molecules, and human leukocyte antigen (HLA)-DR antigens, and the expression was assessed semiquantitatively.

Results. High levels of endothelial E-selectin and proximal tubular expression of HLA-DR antigens, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 were detected in biopsies from cadaveric kidneys, whereas expression of these markers was markedly reduced in LRD kidneys. High levels of tubular antigen expression were significantly associated with traumatic death, prolonged ventilation, and episodes of infection in cadaver donors. Furthermore, the expression of pretransplant tubular antigens in cadaver donor kidneys was significantly associated with early acute rejection following transplantation, suggesting that such kidneys are predisposed to subsequent immune-mediated attack following transplantation.

Conclusions. These results may explain, in part, the superior outcome of LRD allografts compared with cadaver renal allografts.

In clinical renal transplantation, allografts from living-related donors (LRD) have superior graft function and survival compared with cadaver allografts [1–3]. LRD kidneys are obtained from carefully screened, healthy individuals who are genetically related to the recipient, whereas cadaver donor kidneys may undergo abnormal physiological changes associated with brain death, may experience prolonged cold storage times, and may be transplanted into unrelated recipients. In living-unrelated donor (LURD) transplantation, the immunological barriers are similar to those encountered with cadaveric allografts, but the clinical outcome of LURD allografts is significantly better than that of cadaveric transplantation and similar to one haplotype disparate LRD transplants [3–9].

The high success rates of LURD transplantation probably reflects the use of organs obtained under optimal conditions, as there is little genetic advantage over cadaveric transplantation. Furthermore, we have previously demonstrated that immediately following transplantation, cadaver renal allografts may experience a nonspecific inflammatory response associated with prolonged cold ischemia and reperfusion injury [10]. It is possible that early damage to cadaveric organs may render them more susceptible to harmful physiological and immunological events following transplantation.

The effects of the host immune response against the allograft have been studied by analyzing post-transplant biopsies. During episodes of acute rejection, leukocyte infiltration is detected in association with up-regulated expression of adhesion molecules and human leukocyte antigen (HLA) class II antigens [reviewed in 11]. Interestingly, several studies have shown that varying levels of expression of these molecules may be detected in biopsies from cadaver donor kidneys before transplantation [12–18]. However, only a few pretransplant biopsies were analyzed, thus precluding the meaningful analysis of possible donor-derived factors that may be involved in the induction of antigen expression. The presence of high levels of adhesion molecules in the donor kidneys before transplantation provides a mechanism for leukocyte recruitment into the graft and initiation of an alloimmune response.

In this study, we compared the expression of adhesion

Key words: adhesion molecules, rejection, renal transplantation, cadaver organ donors, allografts.

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Table 1. Demographics of donor and clinical parameters following renal transplantation

Clinical parameters	Cadaver (N = 65)	LRD (N =29)
Donor sex (M:F)	33:32	7:22
Donor age *years* ± SD	40 ± 14.7	43 ± 10
Trauma at death[a]	22/65	N/A
Ventilator support *days* ± SD	2.17 ± 1.45	N/A
Episode of cardiac arrest	12/65	N/A
Inotropic support	42/65	N/A
Desmopressin (DDAVP) treatment	18/65	N/A
Donor infection	17/65	N/A
Urine output (final hour) *ml* ± SD	194 ± 197	N/A
Rate of urine output *ml/hr* ± SD	183 ± 110	N/A
Blood urea *mmol/liter* ± SD	5.9 ± 2.7	N/A
Donor serum creatinine *μmol liter* ± SD	94 ± 38	N/A
Donor blood transfusion	16/65	N/A
Local vs. shipped kidney (L:S)	48:17	N/A
Multi/single organ donor (M:S)	56:9	N/A
Cold ischemia time[b] *hours* ± SD	25.1 ± 10.0	1.9 ± 0.5
Delayed graft function[c]	10/65	6/29
Serum creatinine (3 months) *μmol/liter* ± SD	153 ± 51	141 ± 37
Serum creatinine (6 months) *μmol/liter* ± SD	154 ± 48	140 ± 29
No. of rejection episodes (0:1:2:3)[d]	30:22:6:7	12:12:5:0
Rejection by day 7 post-transplantation	11/65	5/29

[a] Traumatic death was defined by the Donating Centre as death resulting from road traffic accidents or other forms of severe physical injury

[b] Significant difference between LRD and cadaver donors ($P < 0.01$)

[c] Delayed graft function was defined as the requirement for dialysis in the first week after transplantation

[d] Acute rejection was defined as an elevation of serum creatinine (>15% above baseline and a response to anti-rejection therapy (98% biopsy proven)

molecules and HLA class II antigens in LRD and cadaver donor kidneys prior to transplantation and related the levels of expression to donor parameters. Furthermore, we investigated whether high levels of antigen expression in kidneys before transplantation were significantly associated with subsequent post-transplant rejection or impaired graft function.

METHODS

Patients and biopsy material

An immunohistochemical analysis was performed on renal biopsies obtained from two groups of renal transplant donors: (*a*) cadaveric donors (N = 65) and (*b*) LRDs (N = 29). Pretransplant wedge biopsies were obtained from kidneys after perfusion and cold storage with hypertonic citrate (Marshall's) solution. As controls, five biopsies were obtained from cadaver donor kidneys at the time of organ retrieval, prior to cold perfusion and storage. Standard triple-therapy immunosuppression (cyclosporine, azathioprine, and steroids) was administered to all transplant recipients [19]. Relevant donor and clinical parameters for cadaver and LRDs are listed in Table 1. Donor data were obtained from kidney donor information forms completed by the donating centers and recipient surgeons and were supplied by the United Kingdom Transplant Support Service Authority (UKTSSA).

Monoclonal antibodies and immunohistochemistry

Seven-micrometer cryostat sections from wedge biopsies were stained using an indirect immunoperoxidase technique as previously described [12]. The sections were stained with monoclonal antibodies, 5D11 (anti–E-selectin), 4B2 [anti–vascular cell adhesion molecule-1 (VCAM-1)], 14C11 [anti–intercellular adhesion molecule-1 (ICAM-1)], which were all obtained from British Biotechnology Ltd. (Oxford, UK), Cyto-DR (HLA-DR; Coulter Immunology, Hialeah, FL, USA), F10.89.4 (anti-CD45 leukocyte common marker) [20], UCHT-1 (anti-CD3 T-cell marker) [21], UCHM-1 (anti-CD14 monocyte/macrophage marker) [22], EBM/11 (anti-CD68 monocyte/macrophage marker) [23], antineutrophil elastase (Dako Ltd., High Wycombe, Bucks, UK) and G1 (anti–P-selectin) [24]. Detection of E- and P-selectin was enhanced by an additional incubation step with a peroxidase-conjugated swine antirabbit Ig (Dako Ltd.), which was preblocked with human AB serum.

Assessment of staining

Semiquantitative staining was scored by two independent observers (S.V.F. and D.D.H.K.) without prior knowledge of the clinical information. Leukocyte infiltration was analyzed with respect to localization in (*a*) the glomeruli (mean number of positive cells per glomerulus per section) and (*b*) intertubular areas (mean leukocyte number per field of view; ×10 objective). The semiquantitative grades given for the endothelial expression of E- and P-selectin were scored as previously described [10]: 0 = negative; 1 = negative with an isolated positive vessel; 2 = focus of positive vessels or occasional positive vessels throughout the biopsy; 3 = multiple foci or a single focus with positive vessels distributed throughout the biopsy. The semiquantitative grading for ICAM-1, VCAM-1, and HLA-DR antigens was based on proximal tubular expression and was scored as grade 0, negative or weakly positive, and grade 1, strongly positive.

Statistical analyses

Univariate analysis using Student's *t*-test, Fisher's exact test, and χ^2 tests was performed to analyze the results of the immunohistological staining with respect to clinical parameters. In view of the large number of comparisons, multiple logistic regression using the SPSS Statistical Program (version 8.0) was performed to determine whether significant univariate associations between elevated antigen expression and possible predictive donor parameters were identified through chance events.

RESULTS

Immunohistological differences between cadaver and living-related donor kidneys

Leukocyte markers. No significant differences were observed in the level of leukocyte infiltration between

cadaveric and LRD kidneys. CD3+ T cells were absent in the majority of donor kidneys, but in occasional biopsies, isolated cells were detected in the interstitium. Both cadaveric and LRD kidneys had high numbers of resident macrophages, with no differences between the two donor groups. In 7 out of 65 (11%) cadaver donor kidneys, a large number of neutrophils were detected in the glomeruli and intertubular areas, but there was no statistically significant difference compared with LRD kidneys.

Endothelial adhesion molecules. Low levels of P-selectin expression were detected on isolated intertubular capillaries in wedge biopsies obtained from both cadaveric and LRD kidneys, with no significant differences in the percentage of kidneys with high levels (≥grade 2) of P-selectin expression (Fig. 1a). In marked contrast, significantly higher levels of intertubular capillary E-selectin expression (≥grade 2) were detected in 35 out of 65 (54%) cadaver donor kidneys compared with LRD kidneys, none of which expressed E-selectin ($P < 0.00001$; Figs. 1b and 2 a, b).

Proximal tubular expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and human leukocyte antigen-DR antigens. Biopsies from cadaveric and LRD kidneys were examined for differences in expression of ICAM-1, VCAM-1, and HLA-DR antigens on the proximal tubules. Constitutive expression of HLA-DR antigens was detected on glomerular endothelium and mesangium, intertubular capillaries, and interstitial leukocytes, as previously reported [13]. However, variable levels of HLA-DR antigens were detected in the cytoplasm and on the membranes of proximal tubules, with strong HLA-DR antigen expression (grade 1) in 43 out of 65 (66%) cadaver donor kidneys, whereas only 2 out of 29 (7%) LRD kidneys were positive for HLA-DR antigens ($P < 0.00001$; Figs. 2 c, d and 3). ICAM-1 expression was detected constitutively at high levels on all vascular endothelium in both the LRD and cadaver donor kidneys. High levels of proximal tubular ICAM-1 expression (grade 1) were detected in 40 out of 65 (62%) cadaver donor kidneys, whereas none of the 29 LRD kidneys expressed tubular ICAM-1 ($P < 0.00001$; Figs. 2 e, f, and 3). Similarly, constitutive expression of VCAM-1 was detected on the Bowman's capsule of all the biopsies analyzed, but in 30 out of 65 (46%) cadaver donor kidneys, high levels of proximal tubular VCAM-1 were detected, whereas all of the 29 LRD kidneys were negative for tubular VCAM-1 ($P < 0.00001$; Figs. 2 g, h, and 3).

Analysis of associations between pairs of adhesion molecule markers (using a χ^2 test with Yates' correction) showed significant associations between high levels of expression of the three tubular markers studied, with the strongest associations between HLA-DR and other markers ($P < 0.0001$). Elevated tubular antigen expression (defined as elevated levels of ICAM-1, VCAM-1, or HLA-DR antigens either alone or in combination) was detected in 50 out of 65 (77%) cadaver kidneys (Fig. 3). No significant associations were observed between elevated tubular antigen expression and high levels of E-selectin expression on the endothelium. There was also no significant association between neutrophil infiltration and elevated E-selectin or tubular antigen expression.

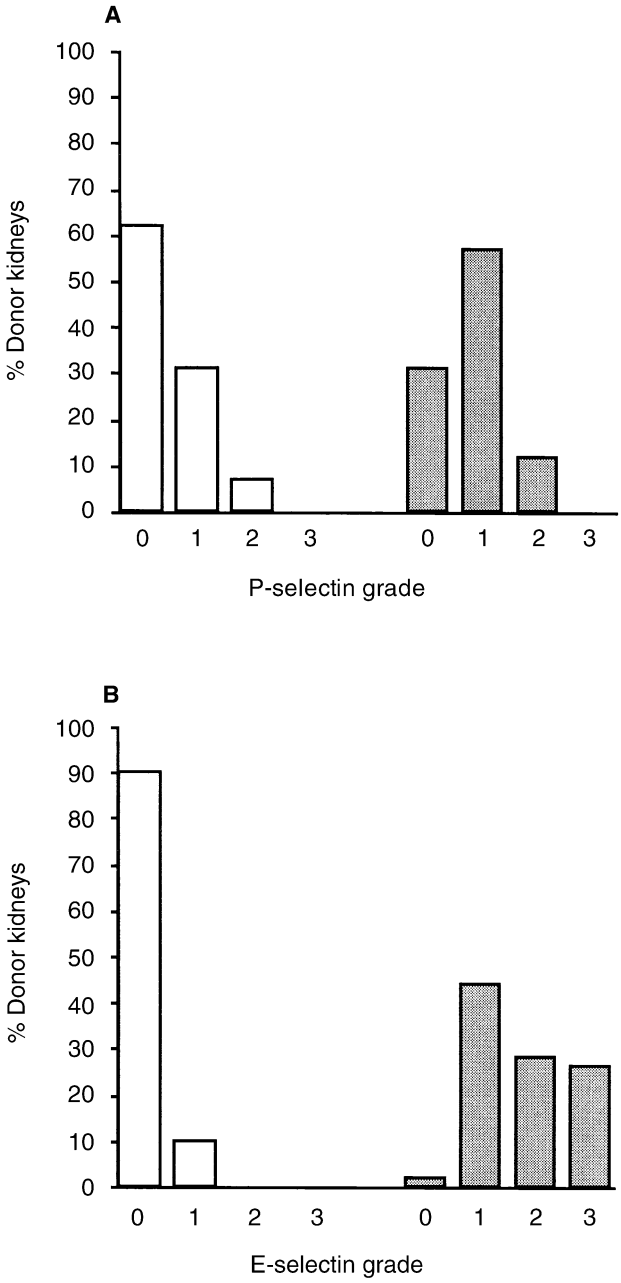
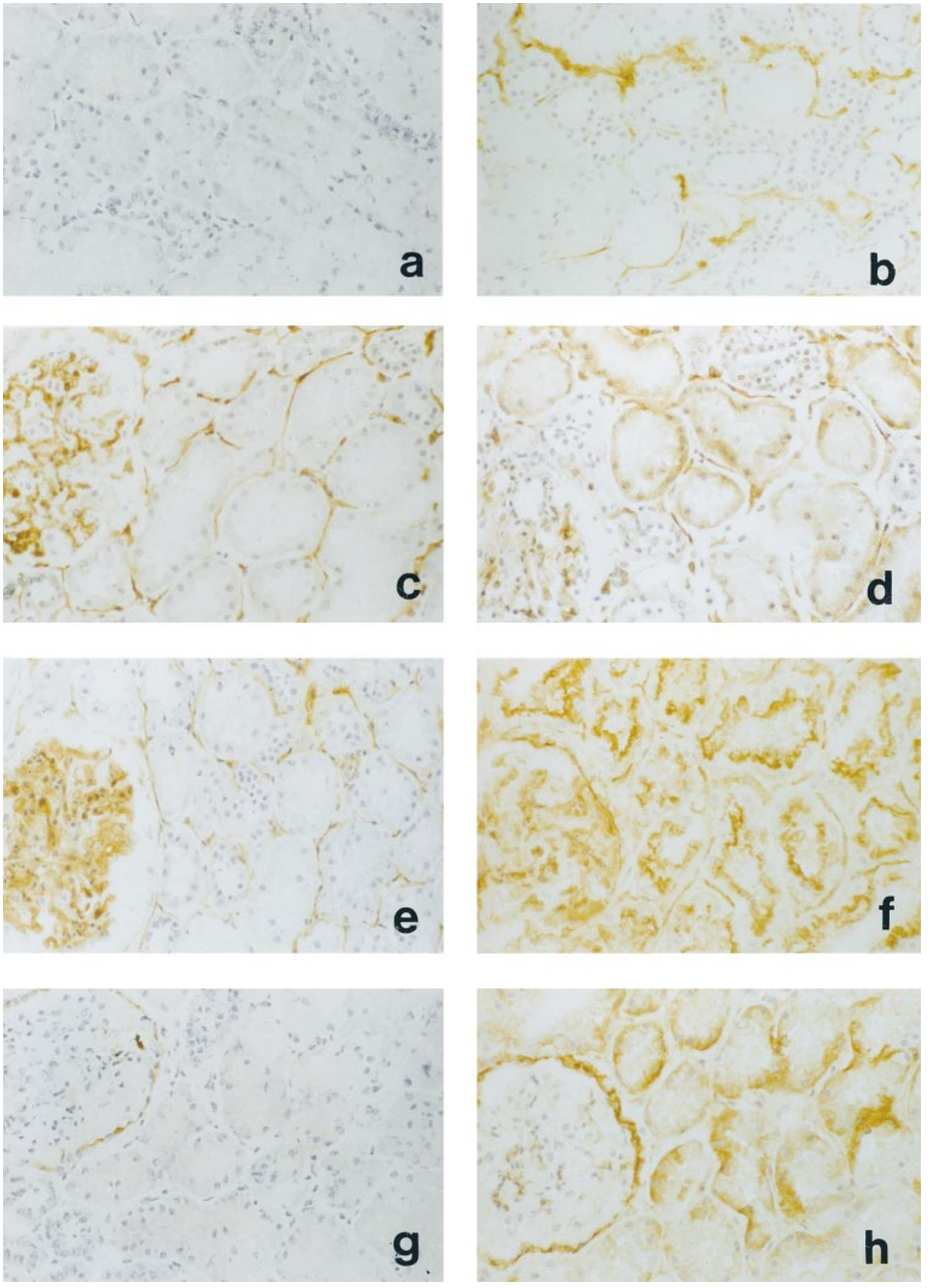


Fig. 1. Levels of P- and E-selectin expression in cadaveric and living-related donor (LRD) kidneys. (*A*) Similar patterns of low level P-selectin expression were detected in cadaveric (■; $N = 65$) and LRD (□; $N = 29$) kidneys. (*B*) High levels of E-selectin expression (≥ grade 2) were detected in 54% of cadaveric kidneys, whereas minimal expression was observed in LRD kidneys.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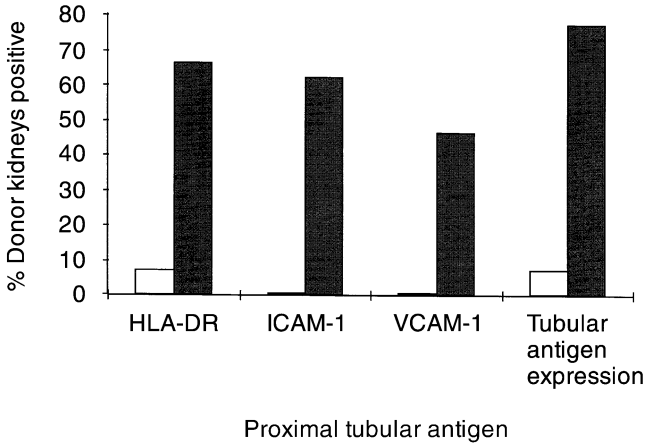

Fig. 3. Expression of HLA-DR antigens, intercellular adhesion molecular-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on the proximal tubules of cadaveric (■; $N = 65$) and living-related donor (LRD; □; $N = 29$) kidneys. High levels of HLA-DR antigens were detected on the proximal tubules of 66% of cadaveric kidneys, whereas only 7% of LRD kidneys had elevated HLA-DR antigen expression ($P < 0.00001$). Elevated ICAM-1 and VCAM-1 expression was detected in 62 and 48% of cadaveric kidneys, respectively, whereas all 29 LRD kidneys were negative for tubular ICAM-1 and VCAM-1 expression ($P < 0.00001$). Elevated tubular antigen expression, defined as expression of either HLA-DR antigens, ICAM-1 or VCAM-1 either alone or in combination, was detected in 50 out of 65 (77%) cadaver kidneys, whereas only 2 out of 29 (7%) LRD kidneys had induced tubular antigen expression ($P < 0.00001$).

Organ retrieval biopsies. No differences in adhesion molecule and HLA-DR antigen expression were detected between biopsies obtained at the time of organ retrieval and subsequent pretransplant biopsies from the same kidneys taken after cold storage. That is, in cases in which expression of these molecules was up-regulated in kidneys at the time of organ retrieval, the appearance was subsequently unchanged following cold storage.

Associations of adhesion molecule and human leukocyte antigen-DR expression with clinical parameters. The expression of high levels of endothelial and tubular antigens in a large proportion of cadaver donor kidneys was analyzed with respect to relevant donor and clinical parameters (Table 1). Statistically significant univariate correlations between clinical parameters listed in Table 1 and elevated expression of endothelial E-selectin or tubular antigens are summarized in Table 2. Multiple logistic regression analysis demonstrated that there was an overall effect of these donor factors on expression of endothelial E-selectin ($\chi^2 = 32.46$, $P = 0.0087$) and tubular antigen induction ($\chi^2 = 27.37$, $P = 0.0375$). The Hosmer-Lemeshow χ^2 test suggested that this model was a reasonable fit. This analysis suggests that the significant univariate associations did not arise through chance because of the number of factors tested.

Table 2. Summary of statistically significant correlations between clinical parameters and high levels of endothelial E-selectin expression or induced tubular antigen expression in cadaveric kidneys

Clinical parameters	Endothelial E-selectin	Tubular antigen
Trauma at death	NS	$P < 0.05$
Ventilator support >3 days	NS	$P < 0.05$
Desmopressin (DDAVP) treatment	$P = 0.015$	NS
Donor infection	NS	$P < 0.05$
Rejection by day 7 post-transplantation	NS	$P < 0.05$

Statistical analyses were performed using Fisher's exact or Student's *t*-test, and confirmed by multiple logistic regression analysis with respect to the large number of comparisons performed. NS is not significant.

Donor parameters

No significant associations were observed between high levels of adhesion molecule and HLA-DR antigen expression with donor age, sex, HLA type, local or shipped kidneys, multi/single organ donors, and cold ischemia time. However, elevated expression of proximal tubular antigens was detected in 20 out of 22 (91%) kidneys from cadaver donors who suffered a traumatic death, whereas it was present in only 30 out of 43 (70%) of cadaver donors who experienced nontraumatic death ($P < 0.05$).

Clinical events in the intensive care unit

In all 15 cadaver donor kidneys with no tubular antigen induction, the period of ventilator support was approximately three days, whereas in 11 out of 50 cadaver kidneys with induced tubular antigen expression, the period of ventilator support was more than three days ($P = 0.041$). Furthermore, in 16 out of 17 (94%) of donors with a recorded incidence of infection, there were elevated levels of proximal tubular antigens, although in 34 out of 58 (59%) of donors with no infection, tubular antigens were also detected ($P < 0.05$). The mean period of ventilation for donors with infection episodes (3.18 ± 2.0 days) was significantly greater than those with no

Fig. 2. Immunohistological differences in adhesion molecule and HLA-DR antigen expression between cadaveric and living-related donor (LRD) kidneys. All biopsies were stained using monoclonal antibodies and were developed by an indirect immunoperoxidase method. (*a*) LRD kidney stained with an anti–E-selectin antibody demonstrating negative expression and (*b*) a cadaveric kidney with high levels of E-selectin on the intertubular capillaries. (*c*) LRD kidney with negative tubular expression of HLA-DR antigens and (*d*) a cadaveric kidney with strong expression of HLA-DR antigens on the proximal tubules. (*e*) Intercellular adhesion molecular-1 (ICAM-1) was absent on the proximal tubules of all LRD kidneys, whereas (*f*) tubular ICAM-1 was detected at high levels in a proportion of cadaveric kidneys. (*g*) Similarly, all LRD kidneys were negative for expression of tubular vascular cell adhesion molecule-1 (VCAM-1), whereas (*h*) a proportion of cadaveric kidneys had high levels of tubular VCAM-1.

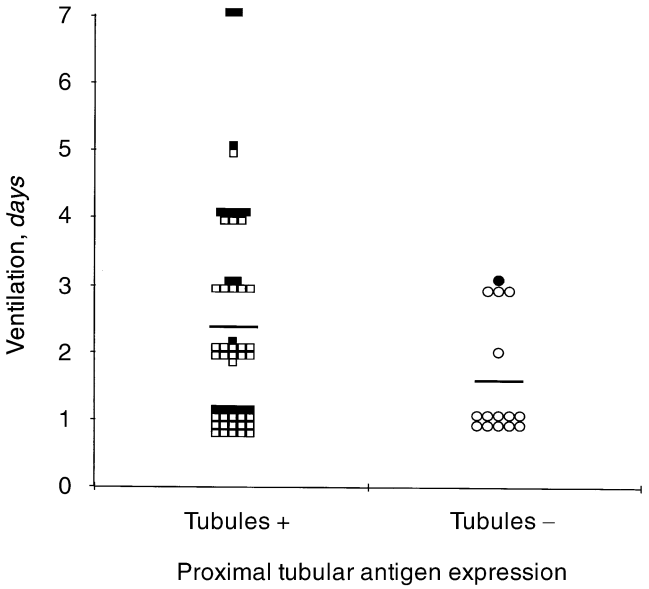

Fig. 4. Relationship between ventilation time, induced tubular antigen expression, and episodes of infection in cadaver donors. The mean period of ventilator support for cadaver donors with induced tubular antigen expression (2.4 ± 1.5 days; □) was higher than that of donors with no tubular antigen induction (1.6 ± 0.9 days; ○). Donors with an episode of infection were also identified with respect to induced tubular antigen expression (■) or no tubular antigen induction (●).

infection (1.83 ± 1.0 days, $P < 0.01$). The relationship between prolonged ventilation, tubular antigen expression, and donor infection is illustrated in Figure 4. There were no significant associations between high levels of adhesion molecules or HLA-DR antigen expression and donor blood transfusions or episodes of cardiac arrest in the donors.

Drug administration

There was a significant association between high levels of E-selectin expression and the administration of desmopressin [(1-desamino-8-D-arginine vasopressin (DDAVP)] to the donor prior to organ retrieval. In 14 out of 18 (78%) donors who received DDAVP, there were high levels of E-selectin expression, whereas E-selectin expression was only detected in 21 out of 47 (45%) donors who did not receive DDAVP ($P = 0.015$). No significant associations were observed between the administration of inotropes and elevated levels of endothelial or tubular adhesion molecule or HLA-DR antigen expression.

Donor renal function

No significant associations were observed with the rate of urine output, volume of urine produced in the final hour, serum creatinine, or urea levels.

Post-transplantation events

Elevated tubular antigen expression was evident before transplantation in all 11 cadaver renal allografts with a biopsy-confirmed acute rejection episode within seven days of transplantation. In contrast, tubular antigens were absent in 15 out of 54 (28%) donor kidneys with no rejection in the first seven days ($P < 0.05$). There were no significant associations with delayed graft function, number of rejection episodes, and three- and six-month serum creatinine levels.

DISCUSSION

The superior graft survival of living donor kidney transplantation compared with cadaver transplantation is partly attributable to the procurement of organs under optimal conditions from healthy donors with minimal ischemia times. In contrast, cadaver donor kidneys experience prolonged periods of cold storage and may undergo traumatic events associated with intensive care management, cause of death, and the abnormal physiological states associated with brain death. The results from this immunohistochemical study demonstrate a striking difference in adhesion molecule and HLA-DR antigen expression between cadaveric and LRD kidneys before transplantation.

High levels of E-selectin expression were detected on the intertubular capillaries of a large proportion of cadaver donor kidneys, whereas E-selectin expression was absent in all 29 LRD kidneys ($P < 0.00001$). Maximal E-selectin expression was observed four to six hours following cytokine stimulation of endothelial cells, returning to basal levels after 24 hours [25]. E-selectin was involved in the initial recruitment of leukocytes to an inflammatory site [26–28] and was up-regulated during allograft rejection [17, 29, 30]. Indeed, we demonstrated that E-selectin expression detected before transplantation is maintained immediately following reperfusion of cadaver renal allografts [10] and thus may facilitate leukocyte-mediated cell damage. Elevated levels of proximal tubular ICAM-1 and VCAM-1 were detected in a proportion of cadaver donor kidneys, whereas all LRD kidneys were negative for tubular adhesion molecule expression ($P < 0.00001$). ICAM-1 and VCAM-1 have been shown to be up-regulated on proximal tubules during renal allograft rejection [14, 17, 18, 29, 31]. Cytokine stimulation of cultured renal tubular epithelial cells demonstrated that ICAM-1 and VCAM-1 expression peaks between one and two days [32, 33], a greater period than required for endothelial E-selectin expression. This difference in kinetic profiles may explain why no significant associations were found between endothelial E-selectin and tubular adhesion molecule expression.

The recruitment of leukocytes by endothelial adhesion molecules has been well characterized [11, 34], but the role of tubular adhesion molecule expression is less clearly defined. *In vitro* data have demonstrated that renal tubular epithelial cells with induced ICAM-1 and

VCAM-1 expression are capable of binding lymphocytes [32, 33, 35]. The induction of tubular adhesion molecule expression may facilitate the infiltration of T lymphocytes into the tubules, resulting in tubulitis, a pathophysiological event associated with allograft rejection. HLA-DR antigens were also detected on the proximal tubules of cadaver donor kidneys, and up-regulated expression was significantly associated with elevated tubular ICAM-1 and VCAM-1 expression ($P < 0.0001$). This supports *in vitro* studies that have shown that tubular HLA class II expression has similar kinetics to tubular ICAM-1 and VCAM-1 expression [35]. It may be surprising that high levels of adhesion molecule expression were detected in the absence of increased levels of leukocyte infiltration, but little is known with respect to immune regulation following brain death. It is probable that following traumatic events in the donor (for example, severe physical injury, infection, brain death), there may be systemic release of cytokines into the circulation, resulting in elevated adhesion molecule expression in peripheral organs but no specific site-directed leukocyte infiltration as detected during allograft rejection or infection. However, the expression of tubular VCAM-1, ICAM-1, and HLA class II antigens in cadaver donor kidneys may render renal allografts more susceptible to cell-mediated attack following transplantation. Indeed, in all 11 cadaver renal allografts with a rejection episode by day 7 post-transplant, high levels of tubular antigen expression were detected pretransplant ($P < 0.05$).

A comparison of biopsies obtained from five cadaver kidneys before and after cold storage demonstrated that antigen expression was detected at the time of organ procurement and was not elevated following cold ischemia. These results suggest that inflammatory responses occur in cadaver donors, probably several hours or days before organ procurement, enabling a sufficient period for transcription and expression of adhesion molecule and HLA-DR antigens. In experimental models of transplantation, induced antigen expression is not detected in donor organs because they are procured from healthy, anesthetized animals that do not experience brain death, a situation similar to that in human LRD transplantation. One of the major differences between living and cadaveric donors is that physiological abnormalities may occur prior to the procurement of cadaver donor organs. Cadaveric donors require careful management of cardiovascular, pulmonary, and homeostatic functions in intensive care, but if stability of vital functions is not maintained, adverse alterations in renal blood flow may result. Animal studies have demonstrated that reduction of blood flow to peripheral organs following brain death may result in ischemic damage [36, 37]. This may be further exacerbated by abnormal rates of oxygen consumption and delivery, leading to anaerobic metabolism, an accumulation of plasma lactate, and reduced oxygen availability to the organs [38, 39].

The secondary effects of brain damage may result in markedly reduced production of vasopressin, leading to diabetes insipidus and loss of homeostatic regulation. Excessive diuresis is controlled with the administration of the L-arginine vasopressin analogue, DDAVP, a powerful antidiuretic [40]. The administration of DDAVP to cadaver donors has proven to be controversial with respect to subsequent renal allograft outcome [41, 42]. Our results have demonstrated that a significant number of cadaveric donors receiving DDAVP treatment had elevated levels of E-selectin expression on the intertubular capillaries. DDAVP has additional properties that enable its use for the treatment of bleeding disorders [43, 44] but may result in cellular damage within a donor organ, as *in vitro* data demonstrate that DDAVP stimulates platelet and endothelial P-selectin expression and increased platelet-activating factor levels on monocytes [45–47]. Therefore, controlling excessive diuresis with DDAVP may result in secondary effects on hemostasis and endothelial activation.

Elevated proximal tubular antigen expression was significantly associated with prolonged ventilator support of cadaver donors. It is widely recognized that patients on prolonged ventilation are susceptible to respiratory tract infections; therefore, unsurprisingly, significant associations were detected between elevated tubular antigen expression and recorded incidences of infection. Our results suggest that the increased risk of infection as a result of prolonged ventilation in the potential organ donor may increase the likelihood of systemic inflammatory events affecting peripheral organs. Another possible explanation may be that patients requiring ventilator support are close to brain death. The physiological effects of brain death on neurological and hormonal functions are well defined, but little is known about the immunological events associated with brain death [reviewed in 48]. However, recent evidence from a rat model of acutely induced brain death demonstrated increased expression of adhesion molecules, multiple histocompatibility complex antigens, inflammatory cytokines, and costimulatory molecules in peripheral organs up to six hours following brain death [49]. Furthermore, dramatic increases in interleukin-6 and severe hormonal imbalances have been detected in blood obtained from patients at the moment of diagnosis of brain death [50]. The results from these studies may explain, in part, the high levels of adhesion molecule and HLA-DR antigen expression in cadaver donor kidneys and not in LRD kidneys. Moreover, we have shown that cadaveric donors who suffered a traumatic death as a result of road traffic accidents or severe physical injury were found to have a significantly higher incidence of tubular antigen expression. Victims of traumatic death may have experienced systemic release of

inflammatory mediators as a response to injury, but in addition, it is possible that this particular group of donors may have suffered acutely-induced brain death.

In summary, we have detected significantly higher levels of adhesion molecule and HLA-DR antigen expression prior to transplantation in a proportion of cadaver donor kidneys, whereas almost all LRD kidneys were negative. Moreover, we have demonstrated a significant association between elevated pretransplant levels of these proinflammatory molecules with early rejection episodes following transplantation. Pretransplant antigen induction may exacerbate the effect of ischemia/reperfusion injury in cadaver renal allografts [10]. These early nonspecific inflammatory events may intensify subsequent alloimmune responses and contribute to the inferior graft outcome of cadaver renal transplantation. By optimizing the conditions for organ retrieval and inhibiting the expression of proinflammatory molecules, it may be possible to improve the results of cadaver renal transplantation toward the success rates observed in LRD transplantation.

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APPENDIX

Abbreviations used in this article are: DDAVP, 1-desamino-8-D-arginine vasopressin; HLA, human leukocyte antigen; ICAM-1, intercellular adhesion molecule-1; LRD, living related donor; LURD, living unrelated donor; VCAM-1, vascular cellular adhesion molecule-1.

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